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TECHNICAL MANUSCRIPT 622

EXPERIMENTAL INFECTION OF MONKEYS WITH BUNYAMWERA AND GERMISTON VIRUSES

Anthony Schwartz
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AUGUST 1970

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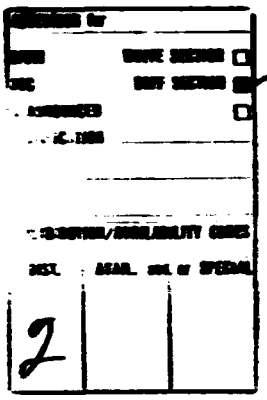

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EXPERIMENTAL INFECTION OF MONKEYS WITH BUNYAMWERA AND GERMISTON VIRUSES

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Virus and Rickettsia Division
BIOLOGICAL SCIENCES LABORATORY

Project 1B562602AD05

August 1970

In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences-National Research Council.

ABSTRACT

Clinical and serological responses investigated in rhesus and cynomolgus monkeys infected with either Bunyamwera or Germiston viruses were generally minimal or absent. A febrile reaction occurred in one of eight monkeys, and another monkey died unexplainably among those given Bunyamwera virus. All monkeys infected with Germiston virus by subcutaneous, intravenous, or intracerebral routes developed fevers, and all infections were relatively consistent in time of onset, duration, and level of viremia. Rhesus monkeys were also susceptible to infection by exposure to aerosolized Germiston virus, although viremias were irregular in these animals and no fevers were detected. Serological responses to infections by Bunyamwera and Germiston viruses (hemagglutination inhibition, complement-fixation, and neutralization tests) provided more reliable indication of infection than clinical response.

I. INTRODUCTION*

Bunyamwera and Germiston viruses are serologically related arboviruses pathogenic for man.[1-5] Mosquitoes have been implicated in the natural transmission of these viruses in endemic areas of Africa,[2,3] but aerosol transmission of Germiston was also suggested in infections of two laboratory workers.[3]

Monkeys sometimes serve as acceptable models for man in studies of infectious diseases, and a search of the literature revealed that some species of monkeys are susceptible to Bunyamwera and Germiston viruses. Smithburn, Haddow, and Mahaffy[6] briefly described experimental infection of rhesus monkeys with Bunyamwera virus, and the Catalogue of Arthropod-Borne Viruses of the World[7] lists both viruses as being infectious for vervet monkeys. This report describes further observations on the infectivity of these viruses and serological responses in simian hosts.

II. MATERIALS AND METHODS

A. VIRUS STRAINS

Both Bunyamwera and Germiston viruses were obtained from the American Type Culture Collection. Bunyamwera virus had undergone 39 suckling mouse brain passages prior to its use in these experiments, and Germiston virus, strain SAAR 1050, was in the 10th suckling mouse brain passage. Seeds were prepared from infected suckling mouse brains as 10% suspensions in borate-buffered saline that contained 50% normal rabbit serum. Concentrations of virus in the inocula were determined by titration and inoculation of weanling mice. The Spearman-Karber method[8] was used for estimating median lethal doses (LD_{50}), which were expressed as decimal exponent (Dex) values.[9]

B. MONKEYS

Rhesus (Macaca mulatta) and cynomolgus (M. irus) monkeys weighing 3.5 to 6 pounds served as experimental hosts for these studies. Only those animals were used in which no neutralizing antibody against either virus could be detected. Monkeys infected by other than the aerosol route were conditioned to restraint in primate chairs for 2 days before inoculation of virus. Rectal thermocouples were attached to a recording potentiometer that automatically recorded internal temperatures at 40-minute

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intervals. Monkeys exposed to aerosolized virus were held individually in ventilated cages to preclude transmission of infectious virus from monkey to monkey by contact or aerosol.

C. ASSAY FOR VIREMIA

Periodically following exposure of the monkeys to virus, blood samples were drawn into syringes wet with heparin and immediately diluted 1:10 in broth. Virus concentrations were determined by inoculating 0.03 ml of each decimal dilution into 10- to 14-g mice by the intracerebral (IC) route and calculating LD_{50} values from the observed deaths.

D. METHOD OF EXPOSING MONKEYS TO INFECTIOUS VIRUS

Monkeys were inoculated with virus intravenously (IV) by the saphenous or cephalic veins, subcutaneously (SC) in the posterior lumbar region, or IC. Those inoculated by the IC route were first anesthetized by IV administration of 2.5% thiamylal sodium (Surital, Parke, Davis); their heads were cleaned of hair, and the scalp and calvaria were perforated with a burr-like drill. Virus was injected through the drilled hole 0.5 inch into the substance of the cerebrum. Exposure of the monkeys to aerosols of virus was accomplished without sedation in a Henderson apparatus that was modified to permit whole-body exposure.[10] Dynamic aerosols were generated for 3 minutes with a Collison atomizer and the cloud was sampled by all-glass impingers. The virus concentrations in the atomizer and impinger samples were determined by assays in mice, and from these data inhaled doses of the aerosolized virus in terms of $MICLD_{50}$ were calculated using Guyton's equation[11] for respiratory minute volume.

E. SEROLOGICAL ASSAYS

Sera obtained periodically following exposure of the monkeys to virus were tested for hemagglutination-inhibiting (HI), complement-fixing (CF), and neutralizing antibodies. Procedures described by Clarke and Casals[12] for the HI test were modified for microtiter equipment. Viral hemagglutinins were prepared by extraction of infected suckling mouse brains with sucrose acetone.[13] Only HI titers greater than 1:20 were considered specific, positive reactions.

CF tests were performed by a technique based on the work of Havens et al.,[14] with modifications for microtiter equipment. Titers greater than 1:4 were considered specific serological responses.

Serum samples taken at indicated intervals were tested for their capacity to neutralize specific virus by the mouse protection test, using constant volumes of undiluted serum and varying dilutions of virus.

Serum-virus mixtures were incubated at 37 C for 30 minutes and then at 4 C for 2 hours. Young adult Swiss-Webster mice (10 to 14 g) were injected intraperitoneally with 0.05 ml of the serum-virus mixture. Log_{10} neutralization indices (LNI) were calculated by subtracting the log_{10} $MIPLD_{50}$ of virus in antiserum from that in normal serum. LNI of 1.5 or greater were considered indicative of a positive serological response.

III. RESULTS

A. BUNYAMWERA VIRUS INFECTIONS

Nine normal young rhesus monkeys each received approximately 600 $MICLD_{50}$ of Bunyamwera virus. Three monkeys were inoculated SC with virus, four IV, and two IC. A mild febrile response with a peak rectal temperature of 103.7 F was observed between the 62nd and 70th hour in one of the four monkeys infected by the IV route. Anorexia and dehydration were apparent from days 4 to 7 in one monkey and severe diarrhea from days 2 to 4 occurred in the other monkey infected by the IC route. All clinical signs were associated with maximal viremic titers.

Only one monkey (RD 9-145) failed to develop a detectable viremia, as indicated by the results in Table 1. Maximum concentrations of virus circulating in the blood varied from 4.7 Dex to more than 6.3 Dex $MICLD_{50}$/ml and occurred between the 3rd and 4th day following administration of virus.

Monkey RD 9-133 was found dead 72 hours after IV inoculation. This monkey had exhibited no overt clinical signs until the 54th hour, when it developed a hypothermia that progressed until death 8 hours later. Necropsy revealed a general appearance of dehydration that might have been accentuated by the 12-hour interval between death and postmortem. The lungs showed some foci of subpleural emphysema and one lesion caused by infestation with the lung mite, Pneumonyssus simicola, but no other gross pathological change was discovered. Selected tissues were frozen as 10% suspensions in saline and stored at -60 C until assayed. Virus concentrations ($MICLD_{50}$/ml) in these tissue suspensions were: brain, 3.5 Dex; lung, 3.5 Dex; heart muscle, 4.0 Dex; heart blood, 4.6 Dex; and liver, 5.1 Dex. Virus titers in heart blood and liver were particularly noteworthy, indicating hepatic involvement and viremia. The samples of virus recovered from these tissues were neutralized by specific anti-Bunyamwera serum.

TABLE 1. VIREMIAS OF MACACA MULATTA INOCULATED WITH BUNYAMWERA VIRUS[a]

Animal Number	Route Inoculated[b]	$MICLD_{50}$ per ml Blood[c] at Indicated Day								
		[3 Hr]	1	2	3	4	5	6	7	8-9
RD 9-145	SC	-	-	-	-	-	-	-	-	-
RD 9-121	SC	-	2.7	4.3	5.7	4.8	4.0	-	-	-
RD 9-122	SC	-	-	4.0	5.3	4.0	3.7	-	-	-
RD 7-48	IV	-	-	-	±	4.1	4.7	4.2	±	-
RD 9-133	IV	-	-	3.7	4.7	Dead				
RD 9-132	IV	-	-	3.0	4.4	4.6	4.8	-	-	-
RD 9-34	IV	-	-	3.7	5.7	5.5	4.5	-	-	-
RD 9-152	IC	-	-	5.3	5.3	4.5	2.8	-	-	-
RD 9-142	IC	-	±	3.7	4.7	≥6.3	≥5.8	3.5	-	-

a. All monkeys received 600 $MICLD_{50}$.
b. SC = subcutaneous; IV = intravenous; IC = intracerebral.
c. Expressed as decimal exponent (Dex); -, no mice died after inoculation with 10^{-1} dilution; ±, only one or two of six mice died after inoculation with 10^{-1} dilution.

Serum samples taken prior to infection and at 6, 13, and 21 days post-infection revealed serologic conversions by HI, CF, and serum neutralization tests for all except monkey RD 9-145 that failed to develop a viremia. The serological results presented in Table 2 revealed that significant levels of HI antibodies were not detectable until after the 6th day of infection and appeared to be maximal by the 13th day in most animals. The 21-day serum sample from the nonviremic monkey (RD 9-145) had an LNI of 1.3, which was not significantly different from that of the preinfection sample (0.6). Thus, monkey RD 9-145 probably did not become infected with Bunyamwera virus.

TABLE 2. SEROLOGICAL RESPONSES OF MACACA MULATTA INOCULATED WITH BUNYAMWERA VIRUS

Animal Number	Route Inoculated	Serum Titers[a] Day 6 HI	Day 13 HI	Day 21 HI	Day 21 CF	Day 21 LNI
RD 9-145	SC	<20	<20	<20	<4	1.3
RD 9-121	SC	<20	160	80	64±	>4.6
RD 9-122	SC	<20	80	80	64	>4.6
RD 7-48	IV	<20	160	80	64	>4.6
RD 9-132	IV	<20	160	80	128	>4.6
RD 9-34	IV	<20	160	160	32	>4.6
RD 9-152	IC	<20	40	80	64	>4.6
RD 9-142	IC	<20	80	160	32±	>4.6

a. Reciprocal of titer by hemagglutination-inhibition (HI) and complement-fixation (CF) tests; the $\log_{10}$ serum neutralization indices (LNI) are in $MIPLD_{50}$. No antibodies to Bunyamwera virus were detectable in sera taken prior to inoculation of virus.

B. GERMISTON VIRUS INFECTIONS IN MONKEYS

A total of four rhesus and three cynomolgus monkeys were inoculated with approximately 8.2 Dex $MICLD_{50}$ of Germiston virus (two rhesus and one cynomolgus by SC route and two of each species by the IV route). This extremely large dose of virus was chosen because we wished to determine the maximum clinical responses that Germiston virus could elicit in these animals. No clinical signs of disease were observed after infection except for febrile reactions, which occurred in all the animals. Rectal temperatures reached maximal levels of 104 to 105 F between 12 and 16 hours after inoculation. By the 30th hour, temperatures of all monkeys returned to normal levels (98 to 102 F) and remained normal through the 10th and last day of observation. The use of primate chairs and a device for continuous and automatic recording of rectal temperatures in these experiments made possible the detection of mild fevers (103 to 104 F) that might otherwise have been obscured by fluctuations of temperatures due to the stress of handling the monkeys.

Virus was detected in the blood immediately after IV inoculation and increased to maximal titers of 5.8 to 7.0 Dex $MICLD_{50}$/ml 12 to 24 hours later (Table 3). In monkeys receiving virus by the SC route, viremias were first detected in the 12-hour samples; titers in these animals also were maximal between the 12th and 24th hours. Viremias persisted until the 3rd and 4th postinoculation day and were undetectable thereafter. Viremias in cynomolgus monkeys appeared slightly higher in titer than those in rhesus monkeys and persisted longer after IV inoculation than after SC inoculation.

TABLE 3. VIREMIAS OF MONKEYS INOCULATED WITH GERMISTON VIRUS

Number of Monkeys[a]	Route[b] of Inoculation	Inoculum, $MICLD_{50}$	Mean $MICLD_{50}$/ml of Blood[c]							
			Hours				Days			
			1	3	12	24	2	3	4	5-10
2R, 1C	SC	$10^{8.2}$	±	2.1	5.5	5.4	4.3	3.5	<2.0	<2.0
2R, 2C	IV	$10^{8.2}$	5.1	4.3	6.0	6.6	4.9	3.3	2.9	<2.0
3R	IC	$10^{4.2}$	ND[d]	ND	ND	4.7	4.2	2.9	<2.0	<2.0

a. R = number of rhesus (M. mulatta); C = number of cynomolgus (M. irus).
b. SC = subcutaneous; IV = intravenous; IC = intracerebral.
c. $MICLD_{50}$, young adult mouse intracerebral LD_{50} expressed as Dex; ±, only one or two mice of six died in lowest dilution tested (10^{-1}); titers of each group were averaged for each sampling interval.
d. ND = not done.

Hematocrit, total and differential white blood cell counts, and sedimentation rates were performed on all the monkeys daily throughout the 10-day observation period. Only hematocrit values varied from accepted normal values. Seven days after inoculation, hematocrit values dropped to an average level of 32.8%, which represented a decrease of 6 to 10% from preinoculation values. However, hematocrit values also decreased in two uninoculated monkeys tested simultaneously, and it is probable that the observed changes were caused by the daily bleedings rather than by the infection with Germiston virus. All monkeys infected with Germiston virus developed LNI of greater than 4.0 by the 21st day.

Three additional rhesus were tested for their responses to infection by the IC route. An inoculum containing 4.2 Dex $MICLD_{50}$ of virus was injected into the cerebrum of each monkey. Fevers were observed in all three between 25 and 40 hours, with maximal temperatures of 102.8 to 103.8 F occurring 28 to 29 hours postinoculation. Viremia occurred in all monkeys from day 1 through day 3 (Table 3), but titers were substantially lower than those of monkeys infected with larger doses by IV or SC routes. Except for the

expected pawing at the head and the depression that occurred within 24 hours after anesthesia and invasion of the calvaria, no signs attributable to encephalitis were detected. One monkey had diarrhea from day 5 to day 7 but responded to routine treatment. Twenty-one days after inoculation each of the three animals had LNI of greater than 6.0.

Accidental infections of laboratory personnel that have been reported for Germiston virus[3] were probably caused by aerosols of the virus. This possibility of aerogenic transmission in man prompted us to investigate the infectivity of aerosolized virus for monkeys. Nineteen rhesus monkeys were exposed to aerosolized Germiston virus at estimated inhaled doses ranging from 2 to 16,000 $MICLD_{50}$. Three monkeys that inhaled an estimated 2 $MICLD_{50}$ and two each that inhaled approximately 16 and 160 $MICLD_{50}$ failed to become infected by the criteria of serological response. The viremic patterns that followed aerogenic infection of 7 of the 12 remaining animals are presented in Table 4, and the serological responses are summarized in Table 5.

TABLE 4. VIREMIAS OF MACACA MULATTA INFECTED WITH AEROSOLIZED GERMISTON VIRUS

Animal Number	Estimated Inhaled Dose, $MICLD_{50}$	Virus Titer per ml Blood at Indicated Day[a/]							
		1	2	3	4	5	6	7	8-10
RD 9-138	160	-[b/]	-	-	-	2.7	3.3	-	-
RD 7-61	300	-	3.3	2.8	±	-	-	-	-
RD 9-115	300	-	-	-	-	-	±	2.8	-
RD 9-119	300	-	2.5	-	2.7	±	±	-	-
RD 9-135	1,600	-	2.7	3.3	3.6	2.8	3.8	-	-
RD 9-140	1,600	-	±	2.8	2.7	-	-	-	-
RD 9-145	1,600	3.0	3.8	3.5	3.0	±	-	-	-

a. Titers expressed as Dex $MICLD_{50}$.
b. -, less than 2.0 Dex; ±, only one or two died of six mice inoculated with lowest dilution (10^{-1}) tested.

TABLE 5. SEROLOGICAL RESPONSES OF MACACA MULATTA INFECTED WITH AEROSOLIZED GERMISTON VIRUS

Estimated Inhaled Dose, $MICLD_{50}$	Viremia/ Exposed[a]	Number Responding Serologically/ Exposed	HI Titer[b]			CF Titer,[b] Day 21	LNI,[c] Day 21
			Day 7	Day 14	Day 21		
2	0/3	0/3	<20	<20	<20	<4	0
16	0/3	1/3	20	160	1,280	4	≥6.0
160	1/3	1/3	<20	80	160	8	4.7
300	3/3	3/3	<20	40-80[d]	10-320	8-16	≥6.0
1,600	2/3	3/3	40-320	320-1,280	160-1,280	32	≥5.2
16,000	1/4	4/4	<20	40-320	80-640	16-32	≥6.0

a. Number of animals that had detectable viremias over total number that were exposed.
b. HI = hemagglutination-inhibition; CF = complement-fixation. Reciprocals of end point dilution: lowest dilutions tested were 1:20 for HI test and 1:4 for CF test. Preinfection sera of all animals were negative by HI and CF tests.
c. Log_{10} neutralization index ($MICLD_{50}$).
d. Range of titers for more than one responding monkey.

Frank clinical signs were not detected. Rectal temperatures of the monkeys, measured daily without the aid of thermocouples and a recording potentiometer, fluctuated over a wide range because of the excitement caused by handling. Throughout the 10-day observation period, temperatures varied from 99.6 to 104 F in both infected and noninfected animals. This range was considered normal under these conditions of stress.

Although other routes of inoculation produced rather consistent patterns of viremia, infection by the respiratory route yielded highly variable patterns of onset and duration. The virus titers in the blood were always relatively low; the highest recorded was 3.8 Dex $MICLD_{50}$/ml of virus. Only 7 of 12 infected animals exhibited viremias of $10^{2.7}$ $MICLD_{50}$/ml or greater. The remaining five monkeys either had trace or no detectable viremic titers.

In the serological responses of monkeys aerogenically infected with Germiston virus, HI antibodies attained titers of 1:80 to 1:1280 at 21 days. HI titers did not appear to be related to dose of virus inhaled. CF titers of samples taken 21 days after exposure by the respiratory route were suggestive of some degree of dose dependence (Table 5), but because of the small number of samples involved, the differences in titers observed between doses were not statistically significant. All infected monkeys developed LNI of at least 4.7 by the 21st day. It was apparent from these results that serological response was the most reliable measure of infection.

C. CONTACT TRANSMISSION EXPERIMENTS

In each of two separate experiments, two uninoculated M. mulatta were seated close to others infected with either Bunyamwera or Germiston virus. Although the uninoculated monkeys were allowed to touch and exchange food with their infected neighbors, none developed demonstrable viremia, fever, or antibodies.

IV. DISCUSSION

Bunyamwera virus elicits a mild infection in rhesus monkeys that appears comparable to that described of a naturally infected man[3] but certainly less severe than that described of an experimentally infected human cancer patient.[5] The death of one monkey that occurred during the viremic phase of injection is unexplained, yet of interest because of similarities with a death described by Smithburn, Haddow, and Mahaffy.[6] Although it was tempting to attribute the death to viral etiology, the lack of gross pathological signs and relatively low virus levels in the tissues of vital organs did not lend any substantial support to this hypothesis. Nevertheless, the higher levels of virus extracted from the liver than from the blood or other tissues indicates that the virus has a greater affinity for the liver than for any other organ in this primate host. Southam and Moore[5] also reported indirect evidence of the affinity of Bunyamwera virus for hepatic tissue. An enlarged liver of a patient with lymphatic leukemia became nonpalpable 2 to 3 weeks after inoculation with Bunyamwera virus, but even though a viral affinity for hepatic tissue may have contributed to the reduction of liver size, other nonviral causes were not completely ruled out.

Although Germiston virus was infectious for rhesus and cynomolgus monkeys, the disease, like that caused by Bunyamwera virus, appeared extremely mild regardless of the dose or route of inoculation. In contrast, the disease described for man is considered acute and incapacitating.[3] The relative ease with which monkeys were infected by aerosol transmission is noteworthy and serves to warn laboratory personnel of the potential hazards associated with this pathogen. However, there appeared to be no contact transmission of the virus from diseased to normal monkeys.

The susceptibility of rhesus monkeys to infections with either Bunyamwera or Germiston viruses and similarities of the diseases elicited to those in man indicate that this animal may serve as an acceptable host for further studies on the pathogenesis of and immunological responses to these viruses in subhuman primates. Certainly further studies are indicated on the tropisms of these viruses in primate tissues. Cross protection between these related viruses has been investigated in monkeys and will be reported in another publication.

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13. ABSTRACT

Clinical and serological responses investigated in rhesus and cynomolgus monkeys infected with either Bunyamwera or Germiston viruses were generally minimal or absent. A febrile reaction occurred in one of eight monkeys, and another monkey died unexplainably among those given Bunyamwera virus. All monkeys infected with Germiston virus by subcutaneous, intravenous, or intracerebral routes developed fevers, and all infections were relatively consistent in time of onset, duration, and level of viremia. Rhesus monkeys were also susceptible to infection by exposure to aerosolized Germiston virus, although viremias were irregular in these animals and no fevers were detected. Serological responses to infections by Bunyamwera and Germiston viruses (hemagglutination inhibition, complement-fixation, and neutralization tests) provided more reliable indication of infection than clinical response.

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